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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/517,310	KOTANI ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *5-7,9-19,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/17/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-23 are currently pending. Applicant's election with traverse of Group I (Claims 1-4, 8, and 20-21) in the reply filed on October 5, 2006 is acknowledged. Applicants further elected to have the SNP at position 421 of SEQ ID NO 1 searched. Applicant timely traversed the restriction (election) requirement in the reply filed on October 5, 2006 by stating that no adequate reasons and/or examples have been provided to support patentable distinctness. This argument has been fully considered but not found persuasive because in a 371 case patentable distinctness does not need to be shown. The only requirement is to break unity of invention. Additionally applicants traversed the election of species requirement on the grounds that the Office has not provided sufficient reasons to support conclusions of patentable distinctness. However it is pointed out that Office Action of September 5, 2006 specifically states on page 6 that the sequence and polymorphic site election requirement is a restriction requirement and should not be construed as an election of species. Thus only the polymorphism at position 421 will be searched. This restriction requirement is now made FINAL.

Claims 5-7, 9-19, and 22-23 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim.

Accordingly, Claims 1-4, 8, and 20-21 have been examined herein.

Priority

2. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Objections

3. Claim 1 is objected to because the claim still recites the step of determining a polymorphism of the amino acid sequence of ABCG2 polypeptide, a non-elected invention. Appropriate amendment to the claim is required.

Claims 2-3 are objected to because the claims still recite polymorphisms that have not been elected. Appropriate amendment to the claim is required.

Claim 20 is objected to because claim still refers to claim 16 which has not been elected. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8, and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Claim 1 is drawn broadly to encompass a method for predicting a drug transport capability of a mammalian cell by collecting a sample from a mammal and determining a polymorphism of the nucleotide sequence of ABCG2. Accordingly the claim encompasses the detection of any polymorphism in the ABCG2 gene. The specification does not teach any polymorphism of the ABCG2 gene. Thus the specification does not disclose and fully characterize the genus of polymorphisms in terms of particular structure or function. The claim also encompasses ABCG2 gene of any mammal. However the specification does not teach the full length sequence of the ABCG2 gene of any mammal.

Claim 20 is drawn broadly to encompass a method for diagnosing a drug sensitivity comprising analyzing a biological sample from any subject and determining the presence or absence of a polynucleotide having a SNP at position 421 of SEQ ID NO 1 wherein the polynucleotide comprises any one of the position of said SNP and consists of at least 10 contiguous nucleotides of SEQ ID NO 1 or a complementary polynucleotide. Accordingly the claims encompasses the detection of fragments of SEQ ID NO 1 which contain position 421 which can read on any gene. Thus the specification does not disclose and fully characterize the genus of fragments of SEQ ID NO 1 which contain position 421 in terms of particular structure or function.

It is noted that the specification does not teach the entire sequence of the ABCG2 gene. However the specification does teach (Table 3) 11 mutations in the ABCG2 gene that result in amino acid substitutions in the ABCG2 protein. Among the polymorphic mutations identified two mutations, G34A and C421A had a high possibility to affect the function of the ABCG2 polypeptide and one mutation C376T coded for a stop codon. The specification teaches that these three mutations can be used to predict drug transport capability. While methods which detect the presence of the nucleotide variation of G34A, C376T, and C421A meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus required by the claims of any variation in the ABCG2 gene.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the

court states that 'An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, 11 members of the genus of ABCG2 gene nucleotide variations have been identified however only two members had a high possibility to affect the function of the ABCG2 polypeptide and one member coded for a stop codon. No additional nucleotide variations have been disclosed in the specification or prior art. Additionally no fragments of SEQ ID NO 1 which contain position 421 are taught. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided for any mutant ABCG2 nucleic acids. Yet, the claims as written are inclusive of a potentially large genus of mutations in the ABCG2 gene. While one could contemplate a nucleotide substitution, deletion or addition at each and every position in the ABCG2 gene, such nucleotide variations are not considered to be equivalent to specific nucleotide variations which can be used to predict drug transport capability. Rather, mutations in the ABCG2 gene which can be used to predict drug transport capability represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the

wild-type gene does not allow the skilled artisan to envision all of the contemplated polymorphisms encompassed by the claimed genus. Conception of the claimed invention cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of potential methods for isolating additional nucleotide variations. As stated in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. LTD*, 25 USPQ2d 1016, one cannot describe what one has not conceived.

For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

5. Claims 1-4, 8, and 20-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising (i) collecting a DNA sample from a human and determining the nucleotide present at position 421 of SEQ ID NO 1 wherein the presence of A at position 421 is indicative of lower excreting capability of the cell does not reasonably provide enablement for methods comprising (i) collecting any type of sample from any mammal, and determining any polymorphism of the ABCG2 gene; and (ii) analyzing a biological sample from any subject and determining the presence or absence of a polynucleotide having a SNP at position 421

of SEQ ID NO 1 wherein the polynucleotide comprises any one of the position of said SNP and consists of at least 10 contiguous nucleotides of SEQ ID NO 1 or a complementary polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claim 1 is drawn broadly to a method for predicting the drug transport capability of a mammalian cell comprising collecting a sample from a mammal and determining a polymorphism in the ABCG2 gene. This claim reads on any type of cell transport (moving in or out), any drug, any mammal, any sample type, and any polymorphism of the ABCG2 gene. Claims 2-3 define the identity and position of a specific mutation (C421A) of the ABCG2 represented by SEQ ID NO: 1. Claim 4 is drawn to various methods which can be used to detect polymorphisms. Claims 8 and 21 are drawn to a specific class of drugs called indolocarbazole compounds. These claims read on any drug that has the indolocarbazole structure. Claim 20 is drawn broadly to a methods for diagnosing a drug sensitivity by determining the presence or absence of a

polynucleotide having a SNP at position 421 and consisting of at least 10 contiguous nucleotides of SEQ ID No: 1 or a complementary sequence. This claim reads on diagnosing any drug sensitivity, any subject, and any biological sample type.

Nature of the Invention

The claims are drawn to methods for predicting a drug transport capability of a mammalian cell and methods for diagnosing drug sensitivity. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches on page 3 that SEQ ID NO 1 represents the ABCG2 gene. It is noted that SEQ ID NO 1 actually only represents the coding regions of the ABCG2 gene and not the entire gene. The specification on page 35 further teaches 2 mutations in the ABCG2 gene (G34A and C421A) that result in amino acid substitutions in the ABCG2 protein that have a high possibility to affect the function of the ABCG2 polypeptide. Additionally the specification teaches that one mutation (C376T) codes for a stop codon and does not even produce a functional protein. The specification does not teach any other variations in the ABCG2 gene which are associated with drug transport capability. The specification also teaches a chemical structure on page 3. The specification states that this structure belongs in the class of indolocarbazole compounds and that the protein encoded by SEQ ID NO 1 confers a selective resistance to indolocarbazole compounds. The specification specifically provides data

on the association between the SNP at position 421 and an indolocarbazole compound called "Compound B". The specification does not teach any other additional indolocarbazole compounds that are associated with the SNP at position 421. The specification further teaches on page 5 that the inventors analyzed genomic DNA extracted from many human cancer cell lines and clinical samples and identified single nucleotide polymorphisms in the ABCG2 gene. Thus the specification does not teach any other types of samples being collected from any other types of mammals other than DNA from humans.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying novel variants in the ABCG2 gene which can be used to predict the transport capability of a drug is highly unpredictable. Knowledge of the sequence of the wild type ABCG2 gene does not allow one to immediately envision additional mutations in the ABCG2 gene that can be used to predict transport capability of drugs. The specification itself exemplifies the unpredictability in the art of identifying mutations that can be used to predict transport capability of drugs. For instance, the specification (Table 3) teaches that 16 SNPs were found in the ABCG2 gene, and 11 of these SNPs resulted in amino acid changes. However out of the 11 SNPs only 2 were found to have a high possibility to affect the function of the ABCG2 polypeptide. The ABCG2 gene is expected to contain many more polymorphisms. However, the specification does not teach a predictable means for identifying additional variations that can be used to predict transport capability of drugs. Without extensive information regarding the structure-function relationship between the ABCG2 gene and cellular

transportation, it is highly unpredictable as to what would be the identity of additional mutant variants that can be used to predict transport capability of drugs. Thus, one cannot readily anticipate the effect of a polymorphism or mutation on the function or activity of the ABCG2 gene or the protein encoded thereby.

Further, it is unpredictable as to whether the results obtained in human subjects could be extrapolated to other mammals. Knowledge that mutations in a gene occur in one mammal (i.e. humans) does not allow one to conclude that this gene, and mutations in this gene will also occur in other mammals. The specification does not teach homologues of the ABCG2 gene in a representative number of different mammals. In the absence of information regarding the functional properties of the ABCG2 gene and the disclosed mutations in this gene, it is unpredictable as to whether the ABCG2 gene, and particularly the C421A mutation, will also be present in other mammals and can be used to predict transport capability of drugs.

It is also unpredictable as to whether the results obtained with Compound B can be extrapolated to other drugs particularly other indolocarbazole compounds. The teachings in the specification are limited to an association between the 3 mutations and the transport capability of Compound B. There are no teachings in the specification regarding how these 3 mutations affect the transport capability of other drugs particularly other indolocarbazole compounds. The post filing date art of Sanchez et al (J Ind Microbiol Biotechnol) teaches that there are hundreds of indolocarbazole derivatives and several of them have entered clinical trials for the treatment of diverse types of cancer. Sanchez further teaches that the distinct structural features of each

type of indolocarbazole derivative results in one of or several of the following mechanisms (a) inhibition of different protein kinase (b) inhibition of DNA topoisomerase or (c) direct DNA intercalation (Page 560). Accordingly, it is unpredictable as to whether the presently claimed method can be used to predict the transport capability of any drug particularly any indolocarbazole compound given the diverse activities of each of these drugs.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches 3 variants in the ABCG2 gene which produce variant ABCG2 polypeptides which can be used to predict transport capability of Compound B. To identify additional variants of the ABCG2 gene which can be used to predict transport capability of Compound B and other types of indolocarbazole compounds would require extensive experimentation. For example, such experimentation may involve sequencing the ABCG2 gene of humans as well as other types of mammals and then comparing which mutations are present in all of groups. Then each group would have to be given different amounts of different indolocarbazole compounds as well as other drugs and the transport capability would have to be determined. Such random, trial by error experimentation is considered to be undue. While methods for sequencing genes are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for mutations that may linked to a specific characteristic of a protein. The results of performing such methodology is highly unpredictable. The specification has provided only an invitation to experiment. The specification does not

provide a predictable means for identifying additional variants of the ABCG2 gene which can be used to predict transport capability of compound B.

Working Examples:

There are no specific examples provided in the specification in which any other variants of the ABCG2 gene were found that could be used to predict transport capability. Additionally there are no specific examples where non-human mammals were used. Further there are no specific examples provided in the specification in which these mutations can be used to predict transport capability of other drugs besides Compound B.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches 3 mutations within the ABCG2 gene that can be used to predict transport capability of Compound B. The specification does not teach a representative number of additional variants of the ABCG2 gene which can be used to predict transport capability. Further the specification does not teach the affect of these mutations on the transport capability of other drugs particularly other types of indolocarbazole compounds. Additionally, the disclosure of a single mammal, humans, in which mutations in the ABCG2 gene can be used to predict transport capability is not representative of the broadly claimed genus of all mammalian subjects. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 8, and 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the goal of the method and the final step do not agree. Claims 1-4 and 8 are drawn to methods for predicting a drug transport capability of a mammalian cell.

However, the claims recite the final step of determining a polymorphism of the nucleotide sequence of ABCG2 gene. The steps listed in the method do not result in predicting a drug transport capability of a mammalian cell. Therefore, it is unclear as to whether the claims are intended to be limited to methods for predicting a drug transport capability of a mammalian cell or methods for determining a polymorphism of the nucleotide sequence of ABCG2 gene.

Claims 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the goal of the method and the final step do not agree. Claims 20-21 are drawn to methods for diagnosing drug sensitivity. However, the claims recite the final step of determining a polymorphism of the nucleotide sequence of ABCG2 gene. The steps listed in the method do not result in diagnosing drug sensitivity. Therefore, it is unclear as to whether the claims are intended to be limited to methods for diagnosing drug sensitivity or methods for determining a polymorphism of the nucleotide sequence of ABCG2 gene.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Prior to setting fourth this rejection it is noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, the process steps of the claimed invention are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language presented in claim 1 of "a method for predicting a drug transport capability" merely sets forth the purpose of the process, but does not limit the scope of the claims. Additionally the claim language presented in claim 20 of "a method for diagnosing a drug sensitivity" merely sets forth the purpose of the process, but does not limit the scope of the claims.

Claims 1 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Imai (Molecular Cancer Therapeutics June 2002).

Regarding Claims 1-20 Imai et al teach a method wherein the entire coding region of the BCRP gene (also called ABCG2) of 124 Japanese volunteers was sequenced. Imai et al further teach that they found 3 polymorphisms of the BCRP gene in the general Japanese population. They were G34A, C376T, and C421A (see Table

3 and Abstract). Imai et al sequenced the entire coding region of the BCRP cDNA (accession number AF103796). The sequence taught by Imai is 2172 bp long and contains a region consisting of the SNP at position 421 and at least 10 contiguous nucleotides of SEQ ID No: 1.

8. Claims 1-4 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Zamber (Pharmacogenetics 1/2003).

Regarding Claims 1-4 and 20 Zamber et al teach a method wherein the entire coding region of the BCRP gene (also called ABCG2) of 222 volunteers was sequenced. Zamber et al further teach that they found 9 polymorphisms of the BCRP gene in 11 different ethnic populations (Abstract). Zamber et al teach that they sequenced the entire coding region of the BCRP cDNA (accession number NM_004827) using the ABI Prism 3700 Automated Sequencer. The sequence taught by Zamber is 4445 bp long and contains a region consisting of SEQ ID NO: 1 (See Alignment and particularly nucleotides 494-2414). Zamber et al further teach one SNP located in exon 5 which is a C421A transversion which results in a Gln141Lys change.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Imai (Molecular Cancer Therapeutics June 2002) in view of Komatani et al (Cancer Research 1/2001).

The teachings of Imai et al are presented above in paragraph 7.

Imai et al does not teach that the C421A SNP of the ABCG2 gene is associated with the drug transport capability of indolocarbazole compounds.

However Komatani et al teach that small differences in the amino acid sequences of the BCRP gene (also known as AGCG2) may explain differences in the transport capability of indolocarbazole compounds in cells (Page 2831).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Imai et al by further seeing if this mutation effects the transport capability of indolocarbazole compounds as suggested by Komatani for the benefit of identifying additional mutations in the BCRP gene that are associated with the transport capability of indolocarbazole compounds. Komatani et al speculates that small changes in the amino acid sequence of BCRP (such as the Gln141Lys change caused by the C421A transversion) cause changes in substrate specificity and may explain why some people are resistant to these drugs (Abstract and page 2831).

10. Claims 8 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zamber (Pharmacogenetics 1/2003) in view of Komatani et al (Cancer Research 1/2001).

The teachings of Zamber et al are presented above in paragraph 8.

Zamber et al does not teach that the C421A SNP of the ABCG2 gene is associated with the drug transport capability of indolocarbazole compounds.

However Komatani et al teach that small differences in the amino acid sequences of the BCRP gene may explain differences in the transport capability of indolocarbazole compounds in cells (Page 2831).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Zamber et al by further seeing if this mutation effects the transport capability of indolocarbazole compounds as suggested by Komatani for the benefit of identifying additional mutations in the BCRP gene that are associated with the transport capability of indolocarbazole compounds. Komatani et al speculates that small changes in the amino acid sequence of BCRP (such as the Gln141Lys change caused by the C421A transversion) cause changes in substrate specificity and may explain why some people are resistant to these drugs (Abstract and page 2831).

Conclusion

11. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571)

272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER